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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,562	12/05/2001	Daniel R. Salomon	20331-00002 (080060-0002)	2653

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,562	SALOMON ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-18,20,22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-18,20,22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO AMENDMENT, REMARKS, IDS, STATUS OF THE APPLICATION AND CLAIMS

1. The amendment, remarks and the information disclosure statement (IDS) and Form PTO-1449 filed 08/07/06 and the supplemental amendment filed 08/08/06, respectively are acknowledged, entered and considered. In view of Applicant's request claims 1, 13, 14, 20 and 22 have been amended and claims 15, 19, 21 and 23 have been canceled. Claims 1-14, 16-18, 20, 22 and 24 are now pending in the application. The objection to the specification and the rejections under 35 U.S.C. 112, first paragraph and 35 U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment to the specification and claims and remarks filed 08/07/06. However, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained for the reasons set forth in the previous Office action.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 16-18, 20, 22 and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nawrocki et al (Transplantation Proceedings, Vol. 28, No. 6, pp. 3538-3539, 1996) taken with Cramer et al (Transplantation Proceedings, Vol. 29, page 616, 1997) and Schmid et al (Eur. Surg. Res., Vol. 30, pp-61-68, 1998) and further in view of Kouwenhoven et al (Transpl. Int., Vol. 13, No. 6, pp. 385-401, 2000)

Applicant's arguments filed 08/07/06 have been fully considered but they are not persuasive. Applicant's characterizes the invention by stating that the claimed invention is directed to a method of ameliorating chronic allograft rejection in a human or animal allograft recipient comprising administering to the recipient in need of such treatment, in combination, a therapeutically effective amount of cyclosporin (CsA) at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 1, currently amended). In another embodiment, the claimed invention is directed

a method of treating chronic allograft rejection in an allograft recipient comprising administering to an allograft recipient a therapeutically effective amount of cyclosporin at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 13, currently amended) is unpersuasive.

Contrary to Applicant's characterization, claim 1 as currently amended is not directed to administering an effective amount of cyclosporin (CsA) i.e., cyclosporin A, rather, claim 1 is directed generally to administering an effective amount of cyclopsporin (i.e., without specifically claiming cyclosporin A) as argued. Also, claim 13 is not directed to a method of treating chronic allograft rejection in an allograft recipient comprising administering to an allograft recipient a therapeutically effective amount of cyclosporin at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 13, currently amended). Rather, claim 13 as currently amended is directed to a method of treating chronic allograft rejection in an allograft recipient comprising administering to an allograft recipient about one to about 16 milligrams of cyclosporin per kilogram of recipient body mass per day and about 0.5 to about 3 milligrams of 2-chlorodeoxyadenosine per kilogram of recipient body mass per week. Thus, Applicant's characterization of independent claims 1 and 13 is not accurate.

Applicant argues by stating that none of the cited references discloses or suggests the administration of a therapeutically effective amount of cyclosporin in combination a therapeutically effective amount of 2-chlorodeoxyadenosine to produce a decrease in cell-mediated immune responses as indicated by decreased numbers of CD8+ T cells in the peripheral circulation as currently claimed in claim 1. Further, Applicant continues by asserting that the cited references that disclose the use of cyclosporin and 2-CdA in combination focus on the problem of acute allograft rejection. This focus is highlighted in the introduction (first paragraph) of Nawrocki et al article which states "Graft rejection has been the main problem in transplantation since the beginning. This reaction is due to differences in histocompatibility against between the donor and organ recipient" is unpersuasive.

Contrary to Applicant's arguments, Applicant has chosen only the first four lines of the first paragraph of Nawrocki et al article. However, on the fifth line, the first paragraph continues by stating "Until now, immunosuppression ha been the only way to achieve **long-term** (emphasis added) graft survival. Most immunosuppressive protocols have maximum effectiveness against T lymphocytes and indirectly against other cellular components of organ rejection". Thus, the term long-term graft survival clearly refers to chronic rejection. Further, as stated in the previous Office action of 06/28/04, the Examiner has clearly indicated that the primary reference of Nawrocki et al discloses like the instantly claimed invention of independent claims 1 and 13 a method and composition thereof for ameliorating or treating chronic allograft rejection in a mammal by administering a therapeutically effective amount of cyclosporin and 2-

chlorodeoxyadenosine (2-CDA), wherein said composition is administered subcutaneously and is efficient to suppress the recipient's B-cell mediated response to the allograft. The reference also discloses a prolongation of cardiac allograft survival in rats (mammals) following combination treatment with 2-CDA and cyclosporin resulting in efficient inhibition of B-cell function including activation, differentiation, and immunolglobulin production as directed to claims 1 and 13 (See e.g., pages 3538 and 3539 and Table I).

Applicant's assertion that the cited references report short-term studies of acute, not chronic rejection is noted. However, the references of Nawrocki et al and Schmid et al teach the use of identical composition/formulation and would therefore be expected to have the identical properties and functions. Thus, the burden is on the Applicant to show that the composition/formulation of Schmid et al reference and Nawrocki et al reference would not be effective in chronic condition (i.e., in chronic allograft rejection) since the prior art and the instant invention use the same combined composition/formulation (i.e., cyclosporin and 2-chlorodeoxyadenosine) with the same amount of dosages for the same purpose of treatment regardless of its stage (i.e., whether chronic or acute).

In regard to Applicant's arguments that the variation of dosage, at best result in an "obvious to try" situation is unpersuasive. Contrary to Applicant's arguments, the secondary reference of Cramer et al discloses a method and composition thereof for ameliorating or treating chronic allograft rejection in a mammal by administering a therapeutically effective amount of cyclosporin and 2-chlorodeoxyadenosine (2-CDA),

wherein the cyclosporin is provided at 5 mg/kg body weight and 2-CDA at 1 mg/kg body weight which overlaps with the claimed ranges of claims 3 and 13 (See e.g., page 616, under Table 1, Group 3). Similarly, on page 61, the secondary reference of Schmid et al discloses the administration of a therapeutically effective amount of cyclosporin orally at 10 mg/kg body weights and 2-CDA at 0.1 mg/Kg body weights. Thus, in view of the secondary references dosages which overlaps with the claimed dosages and in view of Applicant's acknowledgement on pages 9 and 10 which states that the selected dosage level depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. It is within the skill of the art to optimize the dosages, route of administration and duration time by starting doses the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Thus, given the teachings of the secondary references and further as acknowledged on page 22, lines 1-2 in the instant disclosure, one skilled in the art will be able to readily adjust the 2-CDA and cyclosporin dosages, route of administration and duration time relation to a human patient's 2-CDA and cyclosporin dosage, route of administration and duration time to obtain the desired therapeutic effect.

Further, Applicant argues by stating that a proper characterization of the scope and content of the prior art does not support the contention that "one of ordinary skill in the art by administering compounds and/or agents that ameliorate and/or treat chronic allograft rejection would expect to produce a decrease in cell-mediated immune

responses including decreased circulating levels of CD8+ T cells in the peripheral circulation". For support, Applicant cites the references of Iwakoshi et al (J Immunol. 2001 Dec 1, Vol. 167, No. 11, pp. 6623-6630); Adams et al (Philos. Trans. R Soc. Lond B Biol. Sci. 2001 May 29, Vol. 356, (1409), pp. 703-705) and Sho et al (Ann. Surg. 2002 Nov., Vol. 236, No. 5, pp. 667-675) and several case laws. As such, the rejection under 35 U.S.C. 103(a) over the prior art of record is moot in view of the support presented above (i.e., the various reference and case laws cited above) is unpersuasive.

Contrary to Applicant's arguments, the decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cell in the peripheral circulation would not change the outcome of the methods (i.e., methods of ameliorating and/or treating chronic allograft rejections as claimed in claims 1 and 13, respectively). Further, with respect to the limitation of the effect of cellular immune responses, specifically decreasing the levels of circulatory CD8+ T cells as currently amended in claim 1; the reference of Kouwenhoven et al on page 391, right column teaches that the recognition of histoincompatible MHC alloantigens will provide an alloimmune response. In allorecognition, the MHC antigen is bound to the T cell receptor, wherein once the CD4+ T cell is activated, a cascade of events amplifies the alloimmune response which leads to clonal proliferation of alloreactive cells and stimulates CD8+ T cells to develop into mature cytotoxic effector cells which are cytotoxic to the graft cells. Therefore, in view of the above, one of ordinary skill in the art by administering compounds and/or agents that ameliorate and/or treat chronic allograft rejection would expect to produce a

decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cells in the peripheral circulation.

Therefore, for the reasons discussed in the previous Office action and in view of the above, the combined teachings of the prior art makes obvious a method of ameliorating and/or treating chronic allograft rejection by administering effective amount of cyclosporin in combination with 2-CDA and a pharmaceutical formulation for administration thereof including the limitations as currently amended in claims 1 and 13. Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the combined teachings of the prior art method would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Best*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on (571) 272 0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon Weber
Supervisory Patent Examiner

Mohamed/AAM
December 29, 2006